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Development of Quantitative Structure-Pharmacokinetic Relationships

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Quantitative structure–activity relationships (QSAR) relating biological activity to physiochemical descriptors have been successfully used for a number of years. It is also long recognized that pharmacokinetic parameters may play an important and even determinant role in drug action. This prompted several researchers to focus attention to pharmacokinetic parameters as potential descriptors in quantitative drug design. A number of examples of quantitative structure–pharmacokinetic relationships (QSPR) have appeared in the literature.

The present contribution reviews some developments in this field. In particular, a number of concepts and problems are critically discussed, rather than compilations of examples already published in recent reviews. Attention will be paid to the main processes of the pharmacokinetic or toxicokinetic phase in drug action, including absorption, distribution and elimination (biotransformation and excretion).

It is clear that quantitative approaches are of considerable interest to toxicologists, since these methods may contribute to the development of real predictive toxicology.

Introduction to Quantitative Approaches

Since the stimulating work of Hansch (*1,2*) in the beginning of the 1960s, it is clear that the biological activity of chemical compounds can be related quantitatively to their molecular structure. Initially, partition coefficients (log P) have been studied extensively, and this parameter still remains a descriptor of first choice in QSAR work. Large compilations of partition coefficients measured in various solvent systems are available (*3–5*). Many other physicochemical descriptors have been evaluated for their potential use in correlation studies between these descriptors and biological activity (*4–7*). Application of computers (*8–10*) has made it possible to evolve from qualitative (SAR) to quantitative (QSAR) relationships. Although mainly developed by medicinal chemists and used in the field of drug design, these methods apply whenever organic compounds interact in some way with living systems. The QSAR paradigm therefore is of interest to all those working with drugs, food additives, pesticides, biochemical reactants, environmental pollutants and toxic products, since this method provides a tool for the rational design of new and safer drugs and chemicals (*11,12*). Although considerable progress has been made, this ultimate dream has not yet become true. In the scope of the present report we will only briefly discuss the QSAR approach. A number of good introductions in this field can be found in the literature (*3–7, 13–22*). A complete answer to the question on the real successes of QSAR in drug design cannot be given. Most companies keep their secrets carefully, so that a real evaluation of the merits of QSAR is difficult (*23*). A nice example, however, is the success story published by Cramer (*24,25*).

After the first decade of QSAR, around 1975, it became clear that relationships derived from a series of compounds investigated in isolated systems do not apply to *in vivo* situations. Time dependency of the concentration course, i.e., the pharmacokinetics of the drug, has been recognized to be one of the most important factors for this discrepancy between the *in vivo* and *in vitro* situation, and the influence of the factor time on QSAR has been reported (*14,26–28*). Pharmacokinetics of drugs has been studied for some time now (*29–34*) and its importance in quantitative drug design fully accepted, since this subject was included in the program of several recent QSAR symposia (*22,36–39*). A reason interest has only recently been focused on quantitative structure–pharmacokinetic relationships (QSPR) is the lack of data obtained from homologous series of large size. Pharmacokinetic descriptors are dependent on sex, age, race, physical condition, etc. (*35,36*).

Excellent and recent reviews on quantitative structure–pharmacokinetic relationships have been published (*38,40–43*), so we focus our attention on the choice

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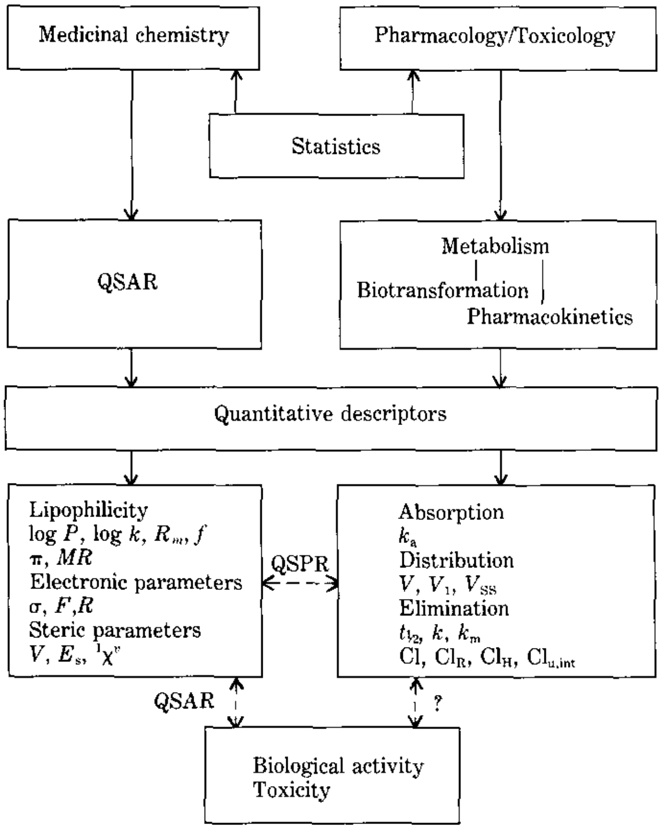

FIGURE 1. Quantitative structure–pharmacokinetic relationships (QSPR): a multidisciplinary effort.

and proper use of pharmacokinetic parameters. Several aspects of the present paper are collected in Figure 1. The following types of equations discussed in this paper are (1) biological activity = f (physicochemical descriptors) and (2) pharmacokinetic parameters = f (physicochemical descriptors).

The first type of equation corresponds to what is now called QSAR, and which we may call QSTR when the toxicity of a product is studied (*44*). It has also been proposed to call this type of relationship QPAR (*45*), quantitative physicochemical–activity relationships. The second type of equation (2) is the topic of the present paper and is abbreviated QSPR (*38,42*). This paper reviews the use of pharmacokinetic parameters, as well as their limitations, in QSPR. Toxicological and pharmacological data can be handled in a similar way in correlations between molecular structure and activity. Therefore all quantitative methods discussed here, i.e., relationships between structure–activity and structure–pharmacokinetics, apply in fact for toxic products as well, and deserve attention of toxicologists. In the following sections we will present first some definitions and concepts and then develop the main processes of the pharmacokinetic (or toxicokinetic) phase. These include absorption, distribution, metabolism and excretion, the last two together referred to as elimination. For each process it will be shown which pharmacokinetic parameters can be obtained, and some of the actual problems of the measurements and their potential application will be discussed.

Some Concepts and Definitions

The established correlation between molecular structure and biological response as obtained from the QSAR approach can be used in two ways. First, to predict the molecular structure producing an optimal response, and second, to find elements allowing an understanding of the mechanisms of action.

A critical step in QSAR is the description of molecular structure by appropriate physicochemical parameters. As stated above, a large number of molecular descriptors have been reported and evaluated. Among these parameters, the partition coefficient (log P, describing the lipophilic and hydrophilic properties) has allowed a large quantity of successful correlations. The reason for this is that distribution processes always, and binding processes often, involve interactions with lipophilic biological environments, such as membranes and receptor sites. Partition coefficients can be determined by the classical shake-flask method. The solvent system most frequently used is *n*-octanol/water for reasons extensively discussed (*46,47*). Chromatographic methods (HPLC, TLC) can also be used advantageously to obtain lipophilic indices (*48–50*). Substituent constants π (*2,4*) and fragmental constants f and f' (*3,4,51*) have been derived from experimental log P values. They allow, with a certain number of corrections for special intramolecular influences, one to predict the hydrophobic behavior of compounds. The shortcomings of these methods have been reviewed by us (*52*). Recently an attempt has been published to explain correction terms used in current fragmental systems with a hydration factor ω (*53*).

The biological response can be a therapeutic one, i.e., desired, or a toxic one, undesired in the case of drugs, desired in the development of insecticides or weedkillers. When molecules produce therapeutic as well as toxic effects, very precious information can be gained by including both therapeutic and toxic responses in the QSAR study. Indeed it is judicious to select from a class the most selective, rather than necessarily the most dose-potent member. The application of this approach to the study of potential antitumor agents (*54*) has been very promising. For instance, this type of study allowed Hansch and Hatheway (*55*) to recommend no further work on triazenes as antitumor agents because the structural features for toxicity could not be separated from those of efficacy. The study of Quinn et al. (*56*) showed the same tendency for 7- and 10-substituted colchicines, potent mitotic inhibitors. That is, decreased toxicity correlates with a simultaneous decrease in potency. However, the same study revealed that the 4-substituted compounds do not obey the correlation established for the 7- and 10-substituted analogs, since they show decreased toxicity for greater antitumor activity. This implies that they have a broader therapeutic range. Although the 4-substituted compounds in this series behave apparently as outliers, they finally made it possible to uncover a promising new synthetic lead. This illustrates that QSAR outliers are of particular interest, a fact that should not be neglected.

The conclusions that can be drawn from a QSAR study depend upon the biological model used. The information content is the highest in biological systems of high level organization. However, this level is associated with a high degree of biological complexity, making the extraction of this information difficult. A current approach is to step down to less complex biological systems. The drawback of such a procedure is the loss of information concerning the coordination of the processes involved in the whole body being the ultimate target for drug use. The complex sequence of the processes determining drug action can be segregated into three distinctive phases: (1) pharmaceutical phase, (2) pharmacokinetic phase, and (3) the pharmacodynamic phase.

The pharmaceutical phase (called exposure phase in toxicology) comprises the factors determining the availability of the drug for absorption, e.g., solubility, complex formation, chemical stability, influence of excipients, etc. It should be kept in mind that these processes can be rate-limiting and that false conclusions may result when they are not taken into account (*57–60*).

The pharmacokinetic (or toxicokinetic) phase includes the processes of absorption, distribution, metabolism and excretion. These processes modulate the concentration-time profile of the substance at the receptor site and consequently are important determinants of drug action. Indeed, lack of activity may not be due to a low affinity of the drug for the receptor, but to an inadequate concentration of the drug at these sites. The introduction of pharmacokinetic parameters accounting for a large part of the complexity of *in vivo* conditions should permit one to interpret the structure–activity correlations in physiological and biological terms. Some confusion exists on the use of pharmacokinetic terms. Recently Di Carlo (*61*) defined metabolism, biotransformation, pharmacokinetics, and toxicokinetics as follows: (Xenobiotic) metabolism is the sum of the processes affecting the fate of a (foreign) substance in organisms, including absorption, distribution, enzymatic and nonenzymatic reactions and excretion. Biotransformation involves the chemistry of enzymatic and nonenzymatic processes. Pharmacokinetics refers to the rate of metabolic processes. Toxicokinetics is used more restrictively when toxic end-products are formed. To illustrate that certain definitions can be used differently, we recall here that for Ariëns, metabolic changes are included in pharmacokinetics (*29*).

The pharmacodynamic (toxicodynamic) phase describes the interaction of the drug with its receptor or other active sites and the resulting response. This phase in drug action can often be investigated in enzyme preparations independently from the preceding phases. A great number of successful QSAR correlations have been obtained using enzyme preparations, i.e., a simple biological model. This type of QSAR has the limitations mentioned above, that is a loss of information compared to a QSAR for the whole body.

There is no doubt that most pharmacokinetic parameters are strongly correlated with lipophilicity (log P). However, one should be careful with the use of certain pharmacokinetic parameters. A number of pitfalls and difficulties will be highlighted in the next section.

Pharmacokinetic Parameters and Their Potential Use in Quantitative Structure–Pharmacokinetic Relationships

Drug Absorption

The definition of the process of drug absorption is more complex than it appears at a first glance. The definition is dependent upon the context of experimental observation. In most cases this may lead to divergent interpretations (*32*). By the most appropriate definition, absorption is the sum of processes by which a drug proceeds from the site of administration to the site from which the drug is transported to the site of action in the body. The most studied routes of absorption are the dermal (*62*) and the gastrointestinal route (*63–65*). The possibilities and problems of percutaneous absorption have been reviewed by Hadgraft (66). In the present paper the discussion on absorption is based on the gastrointestinal route for which a large body of *in vivo* data is available. In an *in vivo* situation, besides the already mentioned limitation by the pharmaceutical phase, four other rate-limiting steps can occur during absorption: mucosal uptake, mucosal metabolism, gastric emptying, and blood flow.

Mucosal uptake and metabolism create differences between luminal disappearance rates and blood appearance rates (*67,68*). The results of *in situ* techniques (*69*) measuring disappearance rates should therefore be checked for eventual mucosal interactions. Intestinal drug absorption is more rapid than from the stomach. The reason for this is the greater surface area combined with a more important blood irrigation of the intestine as compared to that of the stomach. Gastric emptying therefore is a controlling step of the rate of drug absorption (*70,71*). Thus the real influence of lipophilicity on absorption may be blurred by gastric emptying. Once the drug has passed the intestinal membrane, it is carried away by the blood creating “sink conditions” which assure continuous absorption. Highly lipophilic and small polar compounds penetrate so rapidly through the membrane that the draining effect of blood flow becomes the rate-limiting step for absorption (*72*). The decline of the absorption rate for the higher members in a homologous series may therefore not be explained by simple partition models (*73*), but by a physiological limitation, e.g., mesenteric blood flow. The drug must pass the liver before reaching the systemic circulation. Indeed, virtually all blood perfusing the gastrointestinal tissues drains into the liver via the hepatic portal vein. The loss of drug occurring during the first passage of the gastrointestinal membranes and liver is called the "first-pass effect." If this phenomenon is not taken into consideration, false QSAR analysis will result, particularly if the metabolites produced are pharmacologically active. The first-pass loss can be assessed by comparing the pharmacokinetic data of oral administration with those following intravenous dose in which an initial passage of the liver is avoided (*74*). Several methods allowing one to differentiate between preabsorptive, gut epithelial and hepatic first-pass biotransformation have been described (*75*).

An important aspect in QSPR studies is the choice of pharmacokinetic parameters for the description of a physiological process. Some of the parameters are intercorrelated in complex ways, making a nonambiguous interpretation difficult. Absorption of a series of homologs described by the peak plasma level (C_{max}) or the area under the concentration–time curve (AUC) values is often directly correlated with lipophilicity. The problems due to the use of these parameters have been recognized by Notari (*76*). Indeed, the direct comparison of the blood level of chemical analogs fails to take into account that these parameters are the complex result of three pharmacokinetic phenomena. Besides absorption, they contain the process of distribution and elimination [Eqs. (1)–(5)].

$$C = \frac{FDk_a}{V(k_a - k)}\left(e^{-kt} - e^{k_a t}\right) \tag{1}$$

$$FD = (\mathrm{Cl})(\mathrm{AUC}) \tag{2}$$

$$\mathrm{Cl} = kV \tag{3}$$

$$t_{\max} = \frac{\ln(k_a/k)}{k_a - k} \tag{4}$$

$$C_{\max} = \frac{FD}{V}\left(\frac{k_a}{k}\right)^{(k/k_a - k)}_{(k/k_a - k)} \tag{5}$$

where C is the plasma drug concentration (amount/volume), k is the elimination rate, k_a is the absorption rate, F is fraction absorbed and D is dose thus FD is the amount of drug in plasma; V is volume of distribution; Cl is total plasma drug clearance, AUC is the surface under the concentration-time profile; = t_{max} is the time to obtain the maximal plasma drug concentration C_{max}. The symbols conform to those of Rowland and Tucker (*77*).

For the same amount absorbed (FD) and identical rate absorption (k_a) the increase in C_{max} can be due either to a decrease of the volume of distribution (V), the elimination rate constant (k) or a combination of both. Consequently, only when V and k are constant, will the change in C_{max} represent a change in k_a or F.

The separation of absorption and disposition (events following the absorption process) is possible with deconvolution procedures. The simplest of these procedures, permitting assessment of the absorption rate constant, is the graphical method known as the method of residuals. More sophisticated techniques have been reviewed by Cutler (*78*). Another frequently used, but inappropriate, descriptor of absorption in QSAR/QSPR is the percentage of drug absorbed (%abs). It can be demonstrated that the relationship between %abs and log P [Eq. 6] is not correct for extrapolation to high lipophilicities, for which %abs becomes greater than 100%.

$$\log(\%\mathrm{abs}) = a \log P + b \tag{6}$$

Seydel and Schaper (*41*) proposed for first-order absorption kinetics to transform %abs to k_a by the expression (7):

$$k_a = -\ln[1 - (\%\mathrm{abs}/100)]/t \tag{7}$$

Other methods allowing one to determine ka without a complete curve-fitting have been compiled by Tucker (*79*).

Drug absorption has been extensively studied using two- and three-compartment models. For the interested reader we draw attention to a number of reviews (*41–43,80,81*). Here we repeat only that these models revealed a bilinear relationship between drug absorption (log k_a) and lipophilicity (log P) (*80*).

Protein Binding and Distribution

Plasma Protein Binding. Many drugs bind reversibly to plasma proteins, among which mainly plasma albumin, lipoproteins and glycoproteins are involved. The extent of this binding has marked effects on the pharmacokinetics and pharmacodynamics of the drug (*82–84*), since in general only unbound drug can pass through cellular membranes. The influence of binding on the process of distribution, excretion and biotransformation will be discussed below in more detail.

Albumin is the most abundant plasma protein and the most important for plasma protein binding. Albumin binds anionic as well as neutral compounds. Two different binding sites have been identified for albumin. It has been shown (*85*) that drugs binding to site I, also called the warfarin binding site, are generally bulky heterocyclic molecules with a negative charge situated in the center of a largely lipophilic structure. Drugs, however, binding to site II, the indole or benzodiazepine binding site, are mainly molecules with an extended configuration carrying at one extremity a negative charge away from the nonpolar region. Molecular structure determines binding on two levels. First, the structure determines the site to which the compound binds and second influences the binding within a given site. The relationship between molecular structure and binding is difficult to establish when within the studied series of compounds changes occur on both levels. Therefore, most protein binding studies are carried out with homologous series, i.e., compounds which are variations of the same basic skeleton, where there is little chance that the site of binding changes. The methods used to determine drug binding as well as the problems and possibilities in the interpretation of binding data have been extensively reviewed (*41,42*). A large number of relationships between protein binding and molecular structure have been published and recently compiled (*41,42*). It is clear that lipophilicity is the most important determinant of plasma protein binding. Other physicochemical parameters that have been identified to affect protein binding are the electronic properties described by pK_a or Hammett σ values. In most cases, the relationship between the logarithms of the drug/protein association constant K or the ratio fraction bound to unbound drug and $\log P$ is linear, i.e., an increase in lipophilicity produces a proportional increase in binding. Some studies reported parabolic relationships, the optimal $\log P$ varying considerably. This may indicate the influence of structural features. In a similar way, one can interpret the fact that the linear relationship for different series of homologs have approximately the same slope but very different intercepts and cannot be combined into a single regression line (*86*). The structural dependence of protein binding becomes even more apparent when the modification of lipophilicity at different sites of the basic skeleton produces different relationships with $\log P$ (*86*). In conclusion, it can be said that protein binding depends upon lipophilicity and molecular shape.

Volume of Distribution. After absorption the drug is distributed into body fluids and tissues. The extent of distribution can be expressed by the volume of distribution. For drugs equilibrating rapidly throughout the body after intravenous administration, the volume of distribution can be determined by dividing the amount of drug in the body (dose D) by the initial plasma concentration (C_0) obtained from extrapolation to time t_0. The value obtained for the volume ($V = D/C_0$), however, has rarely the physiological meaning of an anatomic space. Therefore, it is called the apparent volume of distribution. This volume has to be considered as a proportionality factor allowing one to calculate the amount of drug in the body for a given plasma concentration. It is not unusual that distribution is a time-dependent process. The drug distributes in this case first into well perfused tissues before poorly perfused regions. Consequently, the volume of distribution is a function of time and can be characterized in different ways.

When drug disposition (distribution and elimination) can be described by a biexponential equation [Eq. (8)], the distribution may be expressed by the following terms: the initial volume of distribution V_1, the volume of distribution at pseudoequilibrium after bolus dose V, and the volume of distribution at steady-state V_{SS}. These volumes and their calculation given by Eqs. (9)–(13).

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \tag{8}$$

$$V_1 = D/(C_1 + C_2) \tag{9}$$

$$V = \mathrm{Cl}/\lambda_2 = D/\lambda_2(\mathrm{AUC}) \tag{10}$$

$$V_{SS} = V_1 \frac{[(C_1'/\lambda_1^2) + (C_2'/\lambda_2^2)]}{[(C_1'/\lambda_1) + (C_2'/\lambda_2)]^2} \tag{11}$$

$$C_1' = \frac{C_1}{(C_1 + C_2)} \tag{12}$$

$$C_2' = \frac{C_2}{(C_1 + C_2)} \tag{13}$$

λ_1 and λ_2 are composed functions of rate constants; the rank-order of magnitudes in the volumes of distribution is $V_1 < V_{SS} < V$.

The question arises which of these volumes is the most appropriate for QSPR studies. V_1 does not describe the entire distribution process, while V is influenced by elimination and tends therefore to overestimate the extent of drug distribution. In contrast, V_{SS} is not affected by changes in drug elimination, reflects the true distribution volume, and hence should be used in QSPR whenever possible.

The volume of distribution is dependent upon, among other factors, the degree of binding to plasma proteins f_u and tissues f_{uR}. A quantitative interpretation of this dependency is possible with the physiological distribution model developed by Øie and Tozer (*87*), which takes into account the presence of proteins within and outside the plasma. In this model the space in which the drug distributes is divided into three physiological volumes: the plasma V_p, the extracellular fluid outside the blood plasma V_E, and the remainder of the total body water V_R. Using the principles of mass balance, Eq. (14) was obtained:

$$V_{SS} = V_P(1 + R_{E/I}) + f_u V_P[(V_e/V_p) - R_{E/I}] + V_R(f_u/f_{uR}) \tag{14}$$

where $R_{E/I}$ is the ratio of the amount of protein in extracellular fluids to that in blood plasma. As demonstrated above, f_u is related to lipophilicity. In order to separate the effect of lipophilicity on distribution from that on plasma protein binding, the unbound volume of distribution (V_{SS}/f_u) is often used. Figure 2, based on Eq. (14), shows that V_{SS}/f_u is not completely independent of plasma protein binding and increases sharply for high binding ($f_u < 0.2$). It can also be noted that the relative increase in unbound volume is dependent upon the degree of tissue binding. Indeed, in the absence of tissue binding ($f_{uR} = 1$), the change from $f_u = 1$ to $f_u = 0.1$ corresponds to an increase of 150% in the ratio V_{SS}/f_u. On the contrary, for drugs highly bound to tissues ($f_{uR} = 0.1$) the same change in f_u increases the unbound volume only by 23%. The relationship between

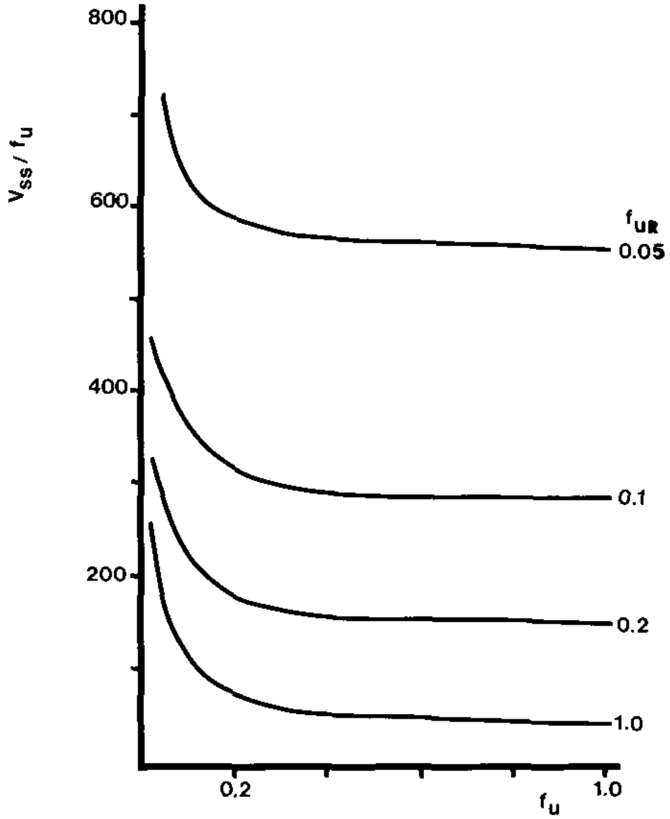

FIGURE 2. Relationship between unbound volume (V_{SS}/f_u) and fraction unbound (f_u) based on Eq. (14), whereby, according to Øie and Tozer (*87*) it is assumed that V_p, V_E, and V_R are 3, 12, and 27 L, respectively, and that $R_{E/I}$ = 1.4.

plasma protein binding and tissue binding cannot be predicted *a priori*. Changes in f_u are not necessarily accompanied by a similar change in f_{uR}. In the case of nonspecific binding, depending only on lipophilicity, however, f_u and f_{uR} are proportional. Consequently, the effect of f_u is counterbalanced by f_{uR} and the unbound volume becomes more or less independent from f_u. The *unbound volume at steady state is therefore in most* cases an appropriate parameter to describe the effect of variations in lipophilicity and distribution within a series of homologs.

Most studies on this subject report a linear relationship between the logarithms of apparent volume of distribution and partition coefficients in homologous series of compounds (*41,42,88*). However, studies using series of compounds and covering a very large range of log P values reveal a nonlinear behavior (*89*). In the range of low log P values, log (V_{SS}/f_u) increases slowly. For high log P values, on the contrary, important changes in log (V_{SS}/f_u) are observed. Figure 3 illustrates this complex relationship between unbound volume (V_{SS}) and lipophilicity (log P) for a series of 5-alkyl-5-ethylbarbituric acids. The model developed by Watanabe and Kozaki (*90*) permits a rationalization of this phenomenon. The *drug distribution at pseudo-equilibrium is modeled by* three compartments (plasma space V_p, lipid space V_1, and nonlipid space V_2) and two equilibrium constants k_1 and k_2, relating the concentration in V_1 and V_2, respectively, to that in V_p. Using the definition of the volume of distribution as the ratio of the sum of the amounts in the three compartments and the concentration in V_p, *the following equation was obtained:*

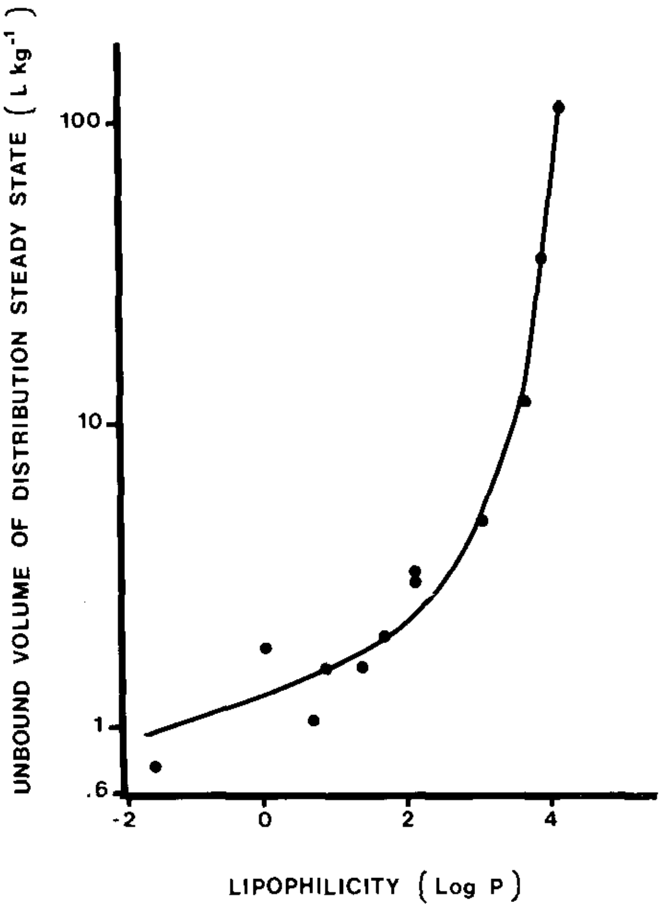

FIGURE 3. Plot of unbound volume of distribution at steady-state (V_{SS}/f_u) in the rat against lipophilicity (log P) of a homologous series of 5-*n*-alkyl-5-ethyl barbituric acids (*89*).

$$V = V_P\,[1 + k_1\,(V_1/V_P) + k_2(V_2/V_P)] \qquad (15)$$

Introducing a linear log-log relationship of the Collander type between k and the partition coefficient P and grouping the constants, this equation simplifies to (*41*):

$$\log V = \log\,(a + bPc) \qquad (16)$$

which clearly shows that the reported linear relationships are special cases of the more general equation (16), the linear relationships being simply the ascending part.

Drug Elimination

The residence of the drug in the body is terminated by *elimination (biotransformation and excretion), the* rate of which is characterized by the elimination half-life ($t_{1/2}$). The latter can generally be taken directly from the log(concentration)–time profile. The elimination half-life has often been used to relate elimination to molecular structure. This application, however, is disputable because the half-life of a drug depends on two other generally independent processes, namely distribution and elimination. This can be seen in Eq. (17):

$$t_{1/2} = \ln 2(V/\mathrm{Cl}) \tag{17}$$

where V is the volume of distribution and Cl the total body clearance. Clearance, in contrast, relates the rate of elimination to the plasma concentration and is a pure descriptor of elimination (*91*). The total body clearance can be determined from the dose absorbed (FD) and total area under the drug concentration–time curve (AUC) [Eq. (2)]. Different organs are responsible for the elimination of drug from the body, the contribution of the liver and kidney being the most important. The total body clearance can therefore be regarded as the sum of the individual organ clearances. If drug elimination is restricted to renal excretion ($\mathrm{Cl_R}$) and hepatic metabolism ($\mathrm{Cl_H}$), the total clearance is described by Eq. (18).

$$\mathrm{Cl} = \mathrm{Cl_R} + \mathrm{Cl_H} \tag{18}$$

In addition to plasma data, allowing the determination of the total clearance, when urine data are available for the estimation of $\mathrm{Cl_R}$, both processes of elimination can be assessed separately. The methods and problems of the measurement of renal clearance have been discussed by Tucker (*92*). Based on mass-balance considerations clearance of an individual organ can be expressed by:

$$\mathrm{Cl} = QE \tag{19}$$

where Q is the blood-flow through the eliminating organ and E is the extraction ratio of the drug. The value of E lies between zero, when no drug is eliminated, and unity, when the drug is completely removed by the organ. One can rationalize from Eq. (19) that clearance becomes limited by blood flow for highly cleared drugs. A deeper understanding of the influence of physiological parameters (e.g., blood flow, protein binding and inherent ability of the organ to extract the drug) on organ clearance can be gained considering the well-stirred model of hepatic clearance (*93,94*):

$$\mathrm{Cl} = \frac{Qf_{\mathrm{ub}}\mathrm{Cl_{u,int}}}{f_{\mathrm{ub}}\mathrm{Cl_{u,int}} + Q} \tag{20}$$

In this equation f_{ub} is the fraction of unbound drug in the blood and $\mathrm{Cl_{u,int}}$ is the intrinsic clearance of unbound drug. With Eq. (20) two extreme situations can be illustrated. First, if the extraction by the organ is very efficient, then $f_{\mathrm{ub}}\mathrm{Cl_{u,int}} >> Q$, and the organ clearance becomes independent of binding and equal to blood flow. This condition can be reached by highly lipophilic members within a congeneric series and has the consequence that any further increase in lipophilicity will not produce an increase of clearance beyond the limiting organ blood flow. In the opposite extreme situation, the organ is very inefficient at removing the drug. Then $f_{\mathrm{ub}}\mathrm{Cl_{u,int}} << Q$, and organ clearance reduces to:

$$\mathrm{Cl} = f_{\mathrm{ub}}\mathrm{Cl_{u,int}} \tag{21}$$

In this case the rate-limiting step is not the blood flow but the organ's intrinsic capacity to eliminate the drug, and clearance becomes dependent on the fraction of unbound drug in the blood. In practice, most drugs fall between these two extremes. Rational QSPR studies should therefore use the intrinsic clearance, which is independent of binding and blood flow, as an index of enzymatic activity. When certain conditions are satisfied the intrinsic clearance can be determined from the dose D and the area under the concentration–time profile (AUC) after oral administration. The first condition is that no extrahepatic clearance is involved, the second is that intestinal absorption is complete. In this case F is equal to $(1 - E)$, where E is the fraction of drug removed by the liver. Consequently, F is the fraction of drug that reaches the systematic circulation and can be expressed by Eq. (22).

$$F = \frac{Q}{(Q + f_{\mathrm{ub}}\mathrm{Cl_{u,int}})} \tag{22}$$

Combining Eq. (20) and (22) shows that under the above mentioned circumstances the oral clearance ($\mathrm{Cl_o}$) is equal to the unbound intrinsic hepatic clearance [Eq. (23)].

$$\begin{aligned}\mathrm{Cl_o} &= D_{\mathrm{o}}/\mathrm{AUC_o}\\ &= \mathrm{Cl}/(1 - E)\\ &= \mathrm{Cl}/F\\ &= f_{\mathrm{ub}}\mathrm{Cl_{u,int}}\end{aligned} \tag{23}$$

However, the restrictions permitting one to establish the above relationship are rarely met. The condition to determine $\mathrm{Cl_{u,int}}$ is therefore the knowledge of binding and blood flow. However, blood flow can be submitted to important inter- and intraindividual variations and its exact assessment in the whole body is difficult. If an investigation of the influence of blood flow and binding is desired the use of isolated perfused liver becomes necessary.

Biotransformation of drugs produces very often several metabolites by different pathways. Generally, the dependency on lipophilicity of metabolite formation varies (*95–97*). A clearer picture can be obtained when the individual metabolite clearances are determined and correlated separately with log P.

Renal excretion is the net result of the processes of filtration, reabsorption, and secretion. Any interpretation of renal clearance data, which can be measured directly (*92*), requires, therefore, the consideration of the different components. For drugs that are only filtered, the renal clearance ($\mathrm{Cl_R}$) is equal to the product

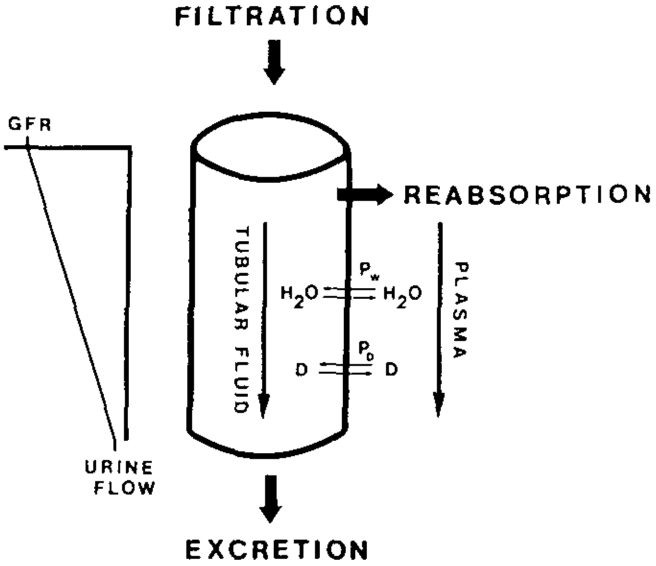

FIGURE 4. Model expressing the urine flow dependence of reabsorption. *Assumptions: each nephron acts as single functional unit;* proximal, distal and collecting tubule have the same reabsorption characteristics; drug is nondissociated and not secreted; P_w = permeability constant of water; P_D = permeability constant of drug. *Then the rate of change of luminal fluid volume is* - P_w, the rate of change of luminal drug concentration is - $P_D(C_u - f_u C_p)$, and

$$\frac{C_{ur}}{C_p} = f_u \left[\frac{(\mathrm{GFR} - Q_{ur})\left(\frac{Q_{ur}}{\mathrm{GFR}}\right)^{[\pi(\mathrm{GFR} - Q_{ur}) - 1]} - \pi}{(\mathrm{GFR} - Q_{ur}) - \pi} \right]$$

where π, defined by the product of the permeability constant of the drug and the tubular surface, is an expression of the tubular permeability for a given compound (*99*).

of the fraction unbound to plasma protein (f_u) and the glomular filtration rate (GFR):

$$\mathrm{Cl_R} = f_u\mathrm{GFR} \qquad (24)$$

Note that only unbound drug is available for filtration. Corrected for the influence of lipophilicity on binding, the unbound renal clearance ($\mathrm{Cl_R}/f_u$) of only filtered drugs is independent of lipophilicity and conforms to the value of GFR. Toon and Rowland (*98*) have shown that this analysis applies to a series of tetracyclines. When the unbound clearance is greater than GFR, secretion must be involved besides filtration. The dependence of secretion upon blood flow and binding is similar to that of hepatic clearance discussed above and expressed in Eq. (20). The renal clearance of drugs with low secretion depends on binding and not on blood flow, whereas for high secretion the inverse can be observed. Reabsorption is a major factor of renal handling. Drug must have been reabsorbed when the unbound renal clearance is smaller than GFR. Reabsorption can be a passive or active process. The latter mechanism is predominant in the reabsorption of vitamins and endogenous compounds, such as electrolytes, amino acids and glucose.

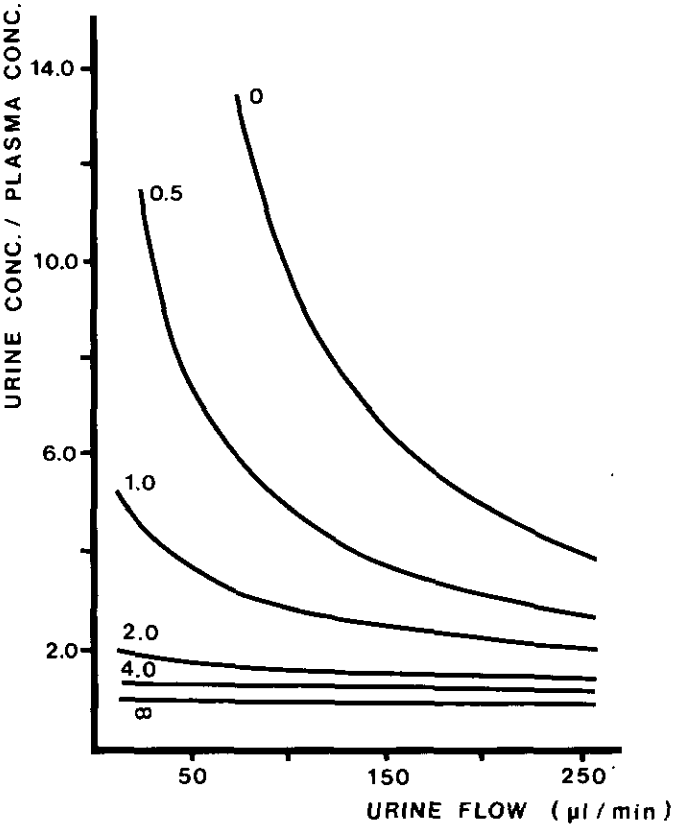

FIGURE 5. Simulation of the effect of permeability on the urine flow dependence of the urine-to-perfusate concentration ratio by use of the expression for C_{ur}/C_p of Fig. 4. For the simulation f_u = 1 and GFR = 1 mL/min (*99*).

The vast majority of drugs are reabsorbed passively, the driving force being the concentration gradient between tubular lumen and plasma created by the renal reabsorption of water. Consequently, the passive diffusion of the drug across the tubular membrane reaches its upper limit when the concentration in the urine C_u becomes equal to the unbound concentration in the plasma C_p. The magnitude of reabsorption of drugs depends not only upon physicochemical characteristics of the substance, e.g., its lipophilicity and degree of ionization, but also upon physiological variables such as extent of reabsorption of water, urine flow, filtration rate and urine pH.

The dependence of renal clearance on urine flow, glomerular filtration rate and fraction unbound can be explained by a simple physiologically based model (*99*). The assumptions allowing the elaboration of this model are recapitulated in Figure 4. The model predicts for drugs for which the tubular membranes are impermeable (π = 0), that the ratio C_u/C_p depends on the ratio GFR/Q_{ur} times f_u. Consequently, for high urine flow rates (Q_{ur}), approaching GFR, the ration C_u/C_p gets close to f_u. For low urine flow, e.g., when 99% of water is reabsorbed, the ratio C_u/C_p is independent of the product f_uGFR. If the tubular is highly permeable ($\pi = \infty$) for the drug, reabsorption rapidly reaches equilibrium and then the ratio C_u/C_p is given by f_u and is independent of urine flow. Figure 5 illustrates in addition to these two extremes the influence of intermediate values of tubular permeability on the reabsorption of unbound drug, assuming a value of 1 mL/min for GFR and f_u equal to 1. A study of the tubular reabsorption of a homologous series of barbituric acids in an isolated perfused rat kidney preparation applies this model (*99*). It was shown that a linear relationship exists up to equilibrium condition between log P and the permeability constant π. The decisive advantage of this model over simple correlations between renal clearance and lipophilicity is its ability to take into account the changes in fraction of drug unbound, glomerular filtration rate and urine flow, which are the major determinants of renal excretion of filtered and reabsorbed drugs.

Urine pH is another important factor of reabsorption. Indeed, only nonionized and sufficiently lipophilic compounds are passively reabsorbed, whereas in general ionized compounds are not. Consequently, the renal clearance of weak acids and bases can be altered considerably when tubular reabsorption is pH-sensitive. This is the case for acids whose pK_a value lies between 3.5 and 7.5 and for bases with pK_a values between 7 and 11. Only a limited number of correlations between drug elimination and molecular structure have been published (*41,42*). Considering the complex physiological situation discussed above, it appears that the choice of biological parameter is crucial for successful correlations. Pharmacokinetic descriptors which are the combination of several basic parameters are called secondary parameters. They can only be used successfully in QSPR when one of the included parameters changes more rapidly with lipophilicity than do the others. Primary parameters, describing only one pharmacokinetic feature, should preferentially be used. Note that the fraction (or percent) of drug excreted unchanged f_e, often used to describe renal clearance, is in fact dependent on nonrenal clearance, as can be shown by equation (25).

$$\begin{aligned} f_e &= \frac{\text{total drug excreted unchanged}}{\text{dose}} \\ &= \frac{\text{rate of excretion}}{\text{rate of elimination}} \\ &= \mathrm{Cl_R/Cl} \end{aligned} \qquad (25)$$

Predictive Toxicology, Another Dream?

In the previous section an overview was given of the possible use of pharmacokinetic parameters in quantitative drug design. As already stated in the introduction, quantitative methods, such as QSAR and QSPR, apply as well for toxicological problems in which we are interested in particular in the present context. We are aware of the fact that this review is far from complete. Therefore the interested reader is referred to the cited literature. In the rest of this section some remarks will be made on the possibilities for using metabolic, i.e., pharmacokinetic and biotransformation, information in predictive toxicology. In other words: is it possible to predict toxicity from molecular structure?

Toxicity is a relative term, since, e.g., pesticides and weed-killers should be toxic for one species and nontoxic for others. The principle of selectivity (*100*) also applies for different tissues within a species and therefore is of great importance for the development of anticancer drugs. A successful application of a quantitative structure–selectivity relationship (QSSR) has been reported for drugs with potential use in cancer therapy (1). Interest in the prediction of toxic activity is growing (*101–105*). A predictive structure–activity model for chemicals that have not yet been subjected to carcinogenesis assays has recently been reported (*106*). In that particular study the products were directly toxic. In other situations bioactivation yields toxic metabolites. Therefore a thorough understanding of the fate of a chemical in a living system, i.e. a detailed knowledge of biotransformation (*107–111*), is a prerequisite in predictive toxicology. The regulation of biotransformation is a recent and important new tool to avoid toxic products. Two concepts, not discussed here, namely the concepts of prodrugs (*112*) and "soft" drugs (*113*), both aimed at a better control of the fate of the drug in the body, are promising and already have proven their applicability. Metabolic routes and pharmacokinetic characteristics can be influenced by the introduction of D,F or CH_3 at certain critical positions in the drug molecule. However, it should not be forgotten that these manipulations may also involve possible changes of physicochemical properties such as lipophilicity (*114,115*). Ariëns (*21*) remarked at a recent symposium summing-up, that examples of quantitative structure–biotransformation relationships are completely lacking. However, like for QSPR, more and more examples have been reported recently (*95,97,116–119*). Several efforts are undertaken to design computer programs that are able to predict metabolic products (*120*). These products in turn, if already known, can be compared with compilations of toxicity data. Potential toxicity can thus be detected in an early stage, and thus suspect functional groups avoided. Clearly, the computer is and will be an important tool for the toxicologist as it became in the 1970s for the medicinal chemist (*8–10*).

Conclusions

In this paper we have used models to describe the complex interdependency of pharmacokinetic parameters. Physiologically based pharmacokinetic modeling (*121*) is a step further to total modeling, describing the whole body by a number of anatomical compartments. In a more general way, simultaneous modeling of the pharmacokinetic and pharmacodynamic phases of drug action has been reported (*122*). If we want to understand the real limiting factors in drug action in the whole body, a stepwise multiple QSAR (MUQSAR) technique should be considered. That is, each step in drug action should be analyzed by using a quantitative method, thus permitting one to fully conceive an overall QSAR. Mathematically this approach can be written as:

$$\text{overall QSAR} = f(\text{QSAR}_i, \text{QSPR}_j, \text{QSBR}_k, \text{QSTR}_l) \quad (26)$$

where i,j,k and $l = 1, \ldots, n$. QSBR and QSTR stand for quantitative structure–biotransformation and structure–toxicity relationships, respectively. This approach is rather time-consuming, and certain practical problems have to be tackled. However, it is our belief that the information finally obtained is worth the effort.

There is little doubt that the introduction of pharmacokinetic parameters in QSAR is a step towards a more rational drug design, that is in the development of drugs and chemicals with an optimal wanted effect and a certain acceptable toxicity-profile, both predicted and understood. As shown in this paper, pharmacokinetic parameters can be useful, but only when used properly.

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